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WO 01/32163 A1

(54) Title: NEW COMBINATION COMPRISING A BETA 2 (β)$_2$ ADRENO RECEPTOR AGONIST AND A LENKOTRIENE RECEPTOR ANTAGONIST

(57) Abstract: The invention provides a pharmaceutical composition, pharmaceutical product or kit comprising a first active ingredient which is a beta2 (β_2) adrenoreceptor agonist and a second active ingredient which is a leukotriene receptor antagonist, for use in the treatment of inflammatory disorders.

NEW COMBINATION COMPRISING A BETA 2 (β_2) ADRENO RECEPTOR AGONIST AND A LENKOTRIENE RECEPTIOR ANTAGONIST

The present invention relates to combinations of pharmaceutically active substances for use in the treatment of inflammatory conditions/disorders, especially respiratory diseases.

There are many different inflammatory mediators implicated in the pathogenesis of respiratory diseases such as asthma. However, drugs that are used to treat respiratory diseases are not always very selective for the pathological features of these diseases. Thus, whilst glucocorticosteroid therapy has been found to be highly effective in the management of asthma, glucocorticosteroids have broad and nonspecific actions and, when taken orally, can produce serious side-effects. Inhaled glucocorticosteroids, on the other hand, are much less likely to cause serious side-effects.

In view of the complexity of respiratory diseases like asthma, it is unlikely that any one mediator can satisfactorily treat the disease alone.

Thus, it would be desirable to develop new pharmaceuticals which can provide a more effective treatment of inflammatory conditions.

In accordance with the present invention, there is therefore provided a pharmaceutical composition comprising, in admixture, a first active ingredient which is a beta2 (β_2) adrenoreceptor agonist selected from formoterol and pharmaceutically acceptable derivatives thereof, and a second active ingredient which is a leukotriene receptor antagonist selected from zafirlukast, montelukast and their pharmaceutically acceptable derivatives.

In the context of the present specification, unless otherwise stated, a pharmaceutically acceptable derivative of formoterol (also known as eformoterol) means a pharmaceutically acceptable ester, salt or solvate of formoterol (e.g. formoterol fumarate) or a pharmaceutically acceptable solvate of such an ester or salt (e.g. formoterol fumarate

dihydrate). A pharmaceutically acceptable derivative of zafirlukast or montelukast should be construed likewise (e.g. montelukast sodium).

Examples of suitable esters include lower alkyl (C_1-C_6 alkyl) esters.

Pharmaceutically acceptable salts include, where applicable, acid addition salts derived from pharmaceutically acceptable inorganic and organic acids such as a chloride, bromide, sulphate, phosphate, maleate, fumarate, tartrate, citrate, benzoate, 4-methoxybenzoate, 2- or 4-hydroxybenzoate, 4-chlorobenzoate, p-toluenesulphonate, methanesulphonate, ascorbate, acetate, succinate, lactate, glutarate, gluconate, tricarballylate, hydroxynaphthalene-carboxylate or oleate salt; and salts prepared from pharmaceutically acceptable inorganic and organic bases. Salts derived from inorganic bases include aluminium, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, manganous, potassium, sodium, zinc and bismuth salts. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic bases include salts of primary, secondary and tertiary amines, cyclic amines like arginine, betaine, choline and the like.

Examples of pharmaceutically acceptable solvates include hydrates.

Certain of the active ingredients used in the present invention are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the active ingredients and mixtures thereof including racemates. Tautomers and mixtures thereof also form an aspect of the present invention.

The invention also provides a pharmaceutical product comprising, in combination, a preparation of a first active ingredient which is a beta2 (β_2) adrenoreceptor agonist selected from formoterol and pharmaceutically acceptable derivatives thereof, and a preparation of a second active ingredient which is a leukotriene receptor antagonist selected from

zafirlukast, montelukast and their pharmaceutically acceptable derivatives, for simultaneous, sequential or separate use in therapy.

In another aspect, the invention provides a kit comprising a preparation of a first active ingredient which is a beta2 (β_2) adrenoreceptor agonist selected from formoterol and pharmaceutically acceptable derivatives thereof, a preparation of a second active ingredient which is a leukotriene receptor antagonist selected from zafirlukast, montelukast and their pharmaceutically acceptable derivatives, and instructions for the simultaneous, sequential or separate administration of the preparations to a patient in need thereof.

It has been found that the choice of active ingredients according to the invention is advantageous because it results in a beneficial anti-inflammatory and bronchodilator effect and, accordingly, can be used to treat various acute and chronic inflammatory conditions/disorders such as chronic obstructive pulmonary disease (COPD); asthma, such as bronchial, allergic, intrinsic, extrinsic and dust asthma, particularly chronic or inveterate asthma (e.g. late asthma and airways hyper-responsiveness); rhinitis and rheumatic arthritis.

The pharmaceutical composition of the invention may be prepared by mixing the first active ingredient with the second active ingredient. Therefore, in a further aspect of the present invention, there is provided a process for the preparation of a pharmaceutical composition which comprises mixing a first active ingredient which is a beta2 (β_2) adrenoreceptor agonist selected from formoterol and pharmaceutically acceptable derivatives thereof, with a second active ingredient which is a leukotriene receptor antagonist selected from zafirlukast, montelukast and their pharmaceutically acceptable derivatives.

The first and second active ingredients may alternatively be administered simultaneously (other than in admixture as described above), sequentially or separately to treat inflammatory conditions. By sequential is meant that the first and second active

ingredients are administered one immediately after the other. They still have the desired effect if they are administered separately but less than about 4 hours apart, preferably less than about 2 hours apart, more preferably less than about 30 minutes apart.

The active ingredients may, and indeed usually will, be used in admixture with one or more pharmaceutically acceptable ingredients which may be selected, for example, from adjuvants, carriers, binders, lubricants, diluents, stabilising agents, buffering agents, emulsifying agents, viscosity-regulating agents, surfactants, preservatives, flavourings and colorants.

For the above-mentioned therapeutic uses the dosages administered will, of course, vary with the first and second active ingredients employed, the mode of administration, the treatment desired and the disorder indicated. However, in general, satisfactory results will be obtained when the total daily dosage of first active ingredient(s) when taken by oral inhalation is in the range from 1 to 50 μg, particularly from 1, 2, 3, 4 or 5 to 48, preferably to 40, more preferably to 24 μg, and the total daily dosage of second active ingredient(s) when taken by oral inhalation is in the range from 1 to 800 μg, particularly from 1, 2, 5, 10 or 20 to 400, preferably to 200 μg.

The pharmaceutical composition, pharmaceutical product or kit according to the invention may be administered as divided doses from 1 to 4 times a day, and preferably once or twice a day.

The first and second active ingredients are conveniently administered topically (to the lung and/or airways) in the form of solutions, suspensions, aerosols and dry powder formulations.

For example metered dose inhaler devices may be used to administer the active ingredient(s), dispersed in a suitable propellant and with or without additional excipients such as ethanol, surfactants, lubricants or stabilising agents.

Suitable propellants include hydrocarbon, chlorofluorocarbon and hydrofluoroalkane (e.g. heptafluoroalkane) propellants, or mixtures of any such propellants. Especially preferred propellants are P134a and P227, each of which may be used alone or in combination with other propellants and/or surfactants and/or other excipients.

Nebulised aqueous suspensions or, preferably, solutions may also be employed, with or without a suitable pH and/or tonicity adjustment, either as a unit-dose or multi-dose formulations.

Dry powder inhalers may be used to administer the active ingredient(s), alone or in combination with a pharmaceutically-acceptable carrier, in the latter case either as a finely divided powder or as an ordered mixture. The dry powder inhaler may be single dose or multi-dose and may utilise a dry powder or a powder-containing capsule.

Metered dose inhaler, nebuliser and dry powder inhaler devices are well known and a variety of such devices are available.

The present invention further provides the use of a pharmaceutical composition, pharmaceutical product or kit according to the invention in the manufacture of a medicament for the treatment of an inflammatory disorder.

Also, the present invention provides a method of treating an inflammatory disorder which comprises administering a therapeutically effective amount of a pharmaceutical composition of the invention to a patient in need thereof.

Still further, the present invention provides a method of treating an inflammatory disorder which comprises simultaneously, sequentially or separately administering:

(a) a (therapeutically effective) dose f a first active ingredient which is a beta2 (β_2) adrenoreceptor agonist selected from formoterol and pharmaceutically acceptable derivatives thereof; and

(b) a (therapeutically effective) dose of a second active ingredient which is a leukotriene receptor antagonist selected from zafirlukast, montelukast and their pharmaceutically acceptable derivatives,

to a patient in need thereof.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

Prophylaxis is expected to be particularly relevant to the treatment of persons who have suffered a previous episode of, or are otherwise considered to be at increased risk of, the disease or condition in question. Persons at risk of developing a particular disease or condition generally include those having a family history of the disease or condition, or those who have been identified by genetic testing or screening to be particularly susceptible to developing the disease or condition.

The present invention will now be further understood by reference to the following illustrative examples. The examples describe certain pharmaceutical compositions which may be prepared as dry powder formulations for oral inhalation.

Example 1

Formoterol fumarate dihydrate	4.5 μg
Zafirlukast	100 μg
Lactose monohydrate	200 - 2000 μg

Example 2

Formoterol fumarate dihydrate	9.0 µg
Zafirlukast	100 µg
Lactose monohydrate	200 - 2000 µg

Example 3

Formoterol fumarate dihydrate	4.5 µg
Zafirlukast	200 µg
Lactose monohydrate	300 - 2000 µg

Example 4

Formoterol fumarate dihydrate	9.0 µg
Zafirlukast	200 µg
Lactose monohydrate	300 - 2000 µg

Example 5

Formoterol fumarate dihydrate	4.5 µg
Montelukast sodium	50 µg
Lactose monohydrate	200 - 2000 µg

Example 6

Formoterol fumarate dihydrate	4.5 µg
Montelukast sodium	100 µg
Lactose monohydrate	200 - 2000 µg

CLAIMS

1. A pharmaceutical composition comprising, in admixture, a first active ingredient which is a beta2 (β_2) adrenoreceptor agonist selected from formoterol and pharmaceutically acceptable derivatives thereof, and a second active ingredient which is a leukotriene receptor antagonist selected from zafirlukast, montelukast and their pharmaceutically acceptable derivatives.

2. A composition according to claim 1, wherein the first or second active ingredient is in the form of a pharmaceutically acceptable salt, ester, solvate or solvate of an ester or salt.

3. A composition according to claim 1 or claim 2, wherein the first active ingredient is formoterol fumarate dihydrate.

4. A composition according to claim 1, wherein the second active ingredient is zafirlukast.

5. A composition according to claim 1, wherein the second active ingredient is montelukast sodium.

6. A composition according to any one of claims 1 to 5 which is formulated for administration by oral inhalation.

7. Use of a composition according to claim 1 in the manufacture of a medicament for the treatment of an inflammatory disorder.

8. A process for the preparation of a pharmaceutical composition as defined in claim 1 which comprises mixing the first active ingredient with the second active ingredient.

9. A method f treating an inflammatory disorder which comprises administering a therapeutically effective amount of a pharmaceutical composition as defined in claim 1 to a patient in need thereof.

10. A method according to claim 9, wherein the inflammatory disorder is asthma or chronic obstructive pulmonary disease.

11. A pharmaceutical product comprising, in combination, a preparation of a first active ingredient which is a beta2 (β_2) adrenoreceptor agonist selected from formoterol and pharmaceutically acceptable derivatives thereof, and a preparation of a second active ingredient which is a leukotriene receptor antagonist selected from zafirlukast, montelukast and their pharmaceutically acceptable derivatives, for simultaneous, sequential or separate use in therapy.

12. A product according to claim 11, wherein the first or second active ingredient is in the form of a pharmaceutically acceptable salt, ester, solvate or solvate of an ester or salt.

13. A product according to claim 11 or claim 12, wherein the first active ingredient is formoterol fumarate dihydrate.

14. A product according to claim 11, wherein the second active ingredient is zafirlukast.

15. A product according to claim 11, wherein the second active ingredient is montelukast sodium.

16. Use of a product according to claim 11 in the manufacture of a medicament for the treatment of an inflammatory disorder.

17. A kit comprising a preparation of a first active ingredient which is a beta2 (β_2) adrenoreceptor agonist selected from formoterol and pharmaceutically acceptable

derivatives thereof, a preparation of a second active ingredient which is a leukotriene receptor antagonist selected from zafirlukast, montelukast and their pharmaceutically acceptable derivatives, and instructions for the simultaneous, sequential or separate administration of the preparations to a patient in need thereof.

18. A kit according to claim 17, wherein the first or second active ingredient is in the form of a pharmaceutically acceptable salt, ester, solvate or solvate of an ester or salt.

19. A kit according to claim 17 or claim 18, wherein the first active ingredient is formoterol fumarate dihydrate.

20. A kit according to claim 17, wherein the second active ingredient is zafirlukast.

21. A kit according to claim 17, wherein the second active ingredient is montelukast sodium.

22. Use of a kit according to claim 17 in the manufacture of a medicament for the treatment of an inflammatory disorder.

23. A method of treating an inflammatory disorder which comprises simultaneously, sequentially or separately administering:
(a) a dose of a first active ingredient which is a beta2 (β_2) adrenoreceptor agonist selected from formoterol and pharmaceutically acceptable derivatives thereof; and
(b) a dose of a second active ingredient which is a leukotriene receptor antagonist selected from zafirlukast, montelukast and their pharmaceutically acceptable derivatives,
to a patient in need thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/02115

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/137, A61K 31/404, A61K 31/47, A61P 29/00, A61P 11/06
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, CAPLUS, EMBASE, MEDLINE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9930703 A1 (ASTRA AKTIEBOLAG), 24 June 1999 (24.06.99)	1-23
X	WO 9839970 A1 (MERCK & CO., INC.), 17 Sept 1998 (17.09.98)	1-23
X	J. Allergy. Clin. Immunol., Volume 104, No 6, 1999, Jean-Francois Dessanges et al, "The effect of zafirlukast on repetitive exercise-induced bronchoconstriction: The possible role of leukotrienes in exercise-induced refractoriness" page 1155 - page 1161	1-23

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 March 2001	14 -03- 2001
Name and mailing address of the ISA Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Eva Johansson/EÖ Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/02115

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	N. Engl. J. Med., Volume 339, No 3, 1988, Jonathan A. Leff et al, "Montelukast, a leukotriene-receptor antagonist, for the treatment of mild asthma and exercise-induced bronchoconstriction" page 147 - page 152 --	1-23
A	Am. J. Med., Volume 109, No 2, 2000, Brian J. Lipworth et al, "Effects of Adding a Leukotriene Antagonist or a Long-Acting Beta2-Agonist in Asthmatic Patients with the Glycine-16 Beta2-Adrenoceptor Genotype" page 114 - page 121 --	1-23
P,A	Chest, Volume 117, 2000, Owen J. Dempsey et al, "Additive Bronchoprotective and Bronchodilator Effects With Single Doses of Salmeterol and Montelukast in Asthmatic Patients Receiving Inhaled Corticosteroids" page 950 - page 953 -- --------	1-23

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/02115

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 9, 10, 23
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE00/02115

Claims 9, 10, 23 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions. (PL 1§)